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Native Type I Collagen is Not a Substrate for MMP2 (Gelatinase A)

To the Editor:

A recent JID paper by Herouy *et al*. (1998) presented some interesting new data on lipodermatoschlerosis. Their interpretations of the data, however, are based upon a single paper in the MMP literature (Aimes and Quigley, 1995), which claims that MMP2 (gelatinase A) is an interstitial collagenase, a claim that we have not been able to confirm. We were the first laboratory to purify, characterize, and clone human MMP2 (Seltzer *et al*, 1981; Collier *et al*, 1988). We found that this proteinase had absolutely no activity against helical collagen. Native helical collagen is defined by its resistance to trypsin cleavage and characteristic viscosity in solution. Subsequent work from our laboratory has shown that MMP2 is an extremely opportunistic proteinase against any collagenous sequence in which the helicity is not perfect. For example, MMP2 cleaves helical type VII collagen within the helical portion of the molecule, but in an area that has relaxed helicity (Seltzer *et al*, 1989). When the Aimes and Quigley paper was published we confirmed our original observations using pure TIMP-free MMP2 and helical collagen shown to be trypsin resistant. Interstitial type I collagen in which the helix was relaxed enough to render it susceptible to trypsin digestion was indeed susceptible to digestion by MMP2. Intact helical collagen was not. Ohuchi *et al* (1997) have recently reconfirmed our original findings.

Cleavage of interstitial collagen by MMP1 yields two characteristic fragments, which lose their helicity at 37°C and become soluble. Therefore, solubilization of type I collagen is not indicative of MMP2 activity, but is of MMP1 activity. Herouy *et al* clearly show active MMP1 in their western immunoblots, indicating that cleavage of labeled type I collagen by their extracts can definitely occur.

It is important to point out that TIMP-MMP complexes have been previously described, but are separated when subjected to SDS-PAGE electrophoresis (Goldberg *et al*, 1989; Wilhelm *et al*, 1989). The high molecular weight band shown in the immunoblots (**Fig 2**) by Herouy *et al* (1998) either are a new type of complex, or represent an artifact of antipeptide antibodies.

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Reply

Lipodermatosclerosis is characterized by distinct morphologic features. Prominent perivascular fibrin cuffs and deposition of hemosiderin pigments due to red blood cell extravasation are major tissue changes occurring in patients with severe chronic venous insufficiency. Perivascular cuffs are highly organized structures primarily composed of fibrin, laminin, fibronectin, tenascin and type I and III collagens (Herrick *et al*, 1992). Fibrous scar tissue associated with fragmentation of elastic fibers and loss of papillary structures at the dermal–epidermal junction are further histologic findings. The dermal–epidermal junction is built up by an extraordinarily complex network of interconnecting proteins such as different collagen subtypes and laminin (Burgeson and Christiano, 1997). To understand the molecular basis of these morphologic alterations